THE PHARMACOLOGY OF MESCALINE

by

Louise Barrett Speck

B.A., University of Pennsylvania, 1938

M.A., University of Denver, 1950

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This Thesis for the Ph.D. degree by

Louise Barrett Speck

has been approved for the

Department of

Physiology

by

Richard H. Whitehead

Clarence A. Maaske

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Speck, Louise Barrett (Ph. D., Physiology)

The Pharmacology of Mescaline

Thesis directed by Professor Richard W. Whitehead

Mescaline, one of the alkaloids found in the peyote cactus, produces colored visions, synesthesias, and alterations of the functioning of the nervous system in human beings. The symptoms of mescaline intoxication have been compared to the symptoms of certain behavior disorders. Investigation of its mode of action seemed worthwhile because its structural formula is similar to epinephrine.

A summary of the results is listed as follows:

1. The intraperitoneal LD50 of mescaline sulfate for nonfasted, male, albino rats was found to be 37 mgm/100 gm body weight with upper and lower confidence limits of 41.0 and 33.2 mgm/100 gm for 19/20 probability.

2. The effects of increasing doses of mescaline did not follow the usual logarithmic dose-effect relationship; ie., maximal heart slowing was found at an intermediate dose. Death was accompanied by flexor convulsions and respiratory arrest.

3. Electroencephalographic investigations indicated that mescaline had an effect similar to epinephrine on cerebral activity. The EEG records became predominantly fast. At intermediate doses bursts of spikes were frequently seen which were not accompanied by muscular activity.

4. Insulin greatly increased the toxicity of mescaline. Epinephrine had a protective effect against the heart slowing and hypoglycemic effects of mescaline but had no influence on the lethality.

5. The effect of various drugs on mescaline action was investigated. Atropine partially prevented the heart slowing in unanesthetized animals but not in the anesthetized animal. Mescaline has an analeptic action against the usual anesthetic dose of pentobarbital, but proved to be too toxic in combination with larger doses of pentobarbital to be useful therapeutically. Decamethonium and curare did not prevent the terminal flexor convulsions in any dose that did not cause death. Phentolamine methane sulfonate modified the terminal convulsions to a clonic type without effect on the lethality. The toxicity of mescaline was increased when it was administered along with physostigmine. Spike activity due to physostigmine and mescaline was not increased when the two drugs were given together.

6. The threshold to electroshock was slightly elevated in confirmation of Tainter's results. Only cocaine and mescaline had this effect among the many central stimulants investigated by Tainter.

7. Some preliminary investigation into the electrolyte effects was attempted. The results were inconclusive due to excessive hemolysis of the samples.

8. An experiment in which a group of rats received daily mescaline injections of 5 mgm/100 gm for a month and a half suggested that mescaline had a general "stressing" effect. No damage to heart, kidney, or brain was observed either grossly or microscopically. Fatty infiltration of the liver was seen microscopically. The adrenals had increased in weight due to marked hyperplasia of the adrenal cortex. The EEG record and heart rate were fast, and moderate hyperglycemia was present at the end of the experiment before the daily injection, whereas

the typical heart slowing and hypoglycemic effect appeared after the daily dose of mescaline had been given. However, the EEG record became slower after mescaline in contrast to the results found in the acute experiments.

It was concluded that mescaline has both peripheral and central effects. It has been suggested that mescaline can compete for epinephrine receptors. There is no indication that mescaline is found in significant concentrations in the brain. Therefore, the central effects may be due to increased circulating epinephrine rather than mescaline itself. The arousal pattern of the EEG, analeptic effect, flexor convulsions, and temporal and occipital lobe disfunction suggest a specific stimulatory effect on the reticular formation and its projections in contradistinction to simple release of the brain stem resulting from inhibition of cortical synapses. Acetylcholine mechanisms may be involved. Mescaline should be useful as a research tool in the investigation of the functioning of the nervous system and of certain behavior disorders.

This abstract of about six hundred words is approved as to form and content. I recommend its publication.

Signed Richard W. Whitehead

Professor Richard W. Whitehead

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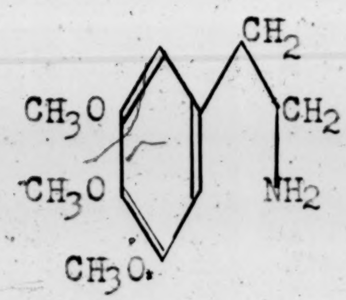
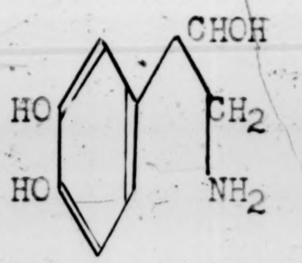
INTRODUCTION

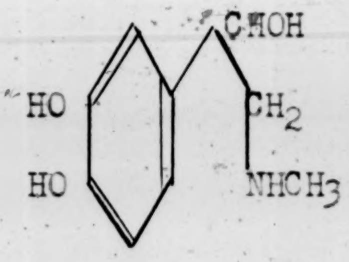
Mescaline is one of the nine alkaloids occurring in the peyote cactus (1). Its main reaction is to produce colored visions, synesthesias, and functional alterations of the autonomic nervous system without disturbance of consciousness. Psychiatrists have used it experimentally to induce temporary psychosis with the hope of gaining insight into the nature of behavior disorders. It has not proved therapeutically useful, but because of the bizarre nature of the psychological response and the structural similarity to norepinephrine and epinephrine, it seemed worthwhile to investigate its mode of action with the hope that it might prove useful as a research tool in the investigation of the functioning of the nervous system.



MESCALINE



NOREPINEPHRINE



EPINEPHRINE

Peyote is a species of small, spineless cactus, classified both as Anhalonium lewinii and Lophophora williamsi, which is found in the arid hills along the lower Rio Grande and southward into Mexico. It is unpretentious in appearance and may be readily overlooked as only the top of the radish shaped plant appears above the ground. The name peyote is a Spanish corruption of the Nahuatl Indian word peyotl which means "Caterpillar" and refers to the downy fuzz at the tip of the plant. Historically it has long been used for ceremonial purposes among the Indian tribes of North and Central America. Sahagun in 1560 was first to describe it as a narcotic cactus used ritually among the Chichimeca. North of the Rio Grande only the sliced-off top or button was used, but southward, the whole plant was cut up and dried for use in religious ceremonies and for medicines.

Among the various Indian tribes it is known by different names such as seni (Kiowa), wokowi (Comanche), and hikori (Tarahumare). The whites incorrectly called it mescal confusing it with the maguey cactus of the Southwestern United States from which the intoxicant mescal is prepared. Further confusion developed in the minds of the whites because the very poisonous red beans of the Sophora secundiflora were called mescal beans, and these were also used ceremonially (2).

The dried tops or buttons of the peyote cactus may be eaten during a ceremony or a decoction may be made from the dried plant. In pre-Columbian times it is thought that peyote was used by the Aztec Indians in their rituals. It has been known to be used in historical times to prevent fatigue during races and battles and to prevent hunger and thirst during journeys across barren and arid regions. Ceremonies making use of peyote south of the Rio Grande feature dancing while in the north prayer and contemplation accompany the eating of the cactus. It is this latter type of ceremony which has been adopted by the North American Church of the American Indian which incorporates precepts both from the aboriginal ceremonies and the Christian religion. The peyote ceremony of the North American Church has spread widely during the last fifty years among tribes of the central and eastern United States. It is favored mostly by the intermediate age groups as the older people have clung to the earlier ideas while the young people have adopted the religion of their white neighbors.

Peyote ceremonies vary somewhat from one Indian tribe to another, but they usually have some features in common. The ceremony is usually held in a specially constructed tipi before a fire enclosed by a crescent shaped mound. A large peyote button is placed upon the mound which is called a "Father Peyote." Following an opening prayer by the priest, four buttons are passed out to each participant. These are eaten to the accompaniment of sacred peyote songs which are sung by each person in the order in which they are seated. The distributions and songs continue until midnight when a particular water ceremony is held. The ritual resumes until daybreak, at which time the morning song is sung and a sacred meal is served. The morning after the ritual is passed in friendly gossip, followed by a feast at noon. There are no dances at these dignified ceremonies, and the spirit is one of friendliness and reverence (2,3).

The chemistry of the plant was investigated in 1888 by the German chemist, Lewin. Between 1894 and 1923 all the alkaloids were extracted from the plant and identified chemically by German chemists such as Käuder, Späth, Becke, and Heffter. In a short time these people had also synthesized all the members of the series as well as a number of analogues. As a result of these investigations, it was felt that the alkaloid mescaline which was present in greatest quantity was the substance responsible for the effects of peyote intoxication. However, it is generally agreed that some of the other alkaloids present undoubtedly modify the reaction.

Peyote was first described from a physiological and psychological point of view by Prentiss and Morgan (4), Weir Mitchell (5), and Havelock Ellis (6). Their observations concerning the psychotic nature of the hallucinations and autonomic reactions sparked considerable interest in the drug. LaBarre(2) states that as a result it was tried as a sedative for the insane, to rouse melancholic and stuperous patients, and in neurasthenia, hysteria, and asthma. Again, according to LaBarre(2), peyote was employed by Briau in anxiety states. Different mescal reactions were found by Bensheim (2) in cycloids and schizoids. Experiments were conducted with the blind and with amputees (47,54). All these investigations produced very interesting but variable results, and as a therapeutic agent, peyote was dropped from the pharmaceutical market. New interest was aroused when synthetic mescaline sulfate became available, and from 1930 to the present time it has been used sporadically to study experimentally induced psychoses. The results with the pure alkaloid are less variable, but otherwise, they seem to be similar to those of the peyote button. Some physiologists have occasionally experimented with the drug, and biochemists sometimes have included it in experiments with other amines. In the following pages the work that has been done with mescaline to date will be reviewed.

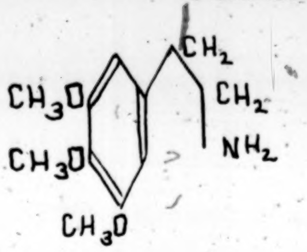
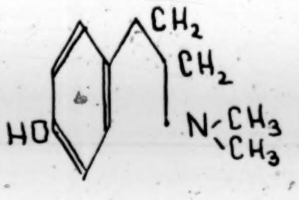
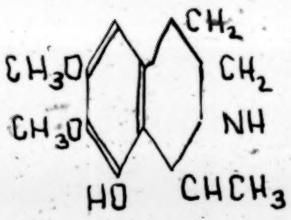
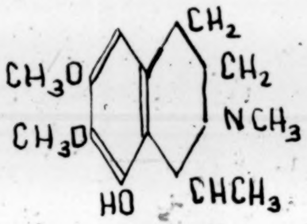
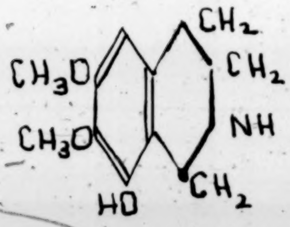
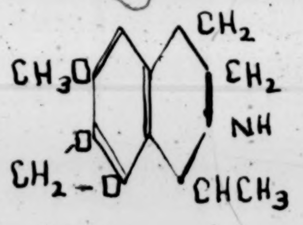
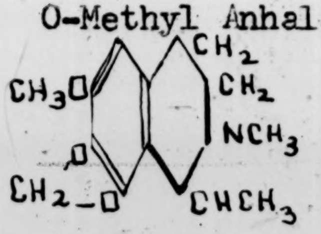
ISOLATION, EXTRACTION, SYNTHESIS:

Numerous cacti contain alkaloids, but mature Lophophora or peyote contains at least nine. The immature plant contains only Pellotine(2). These compounds fall into two classes pharmacologically as some possess a strychnine-like action producing reflex irritability, and others have a morphine-like sedative effect. They were arranged in a scale with mescaline at the morphine-like extreme and lophophorine at the strychnine-like extreme by LaBarre(2); mescaline, pellotine, anahaline, anhaline, anhalamine, anhalonidine, anhalonine, and lophophorine. The effects are variable as peyote is a mixture of all these substances, and the buttons are eaten continuously throughout the night. Generally speaking, it is believed that strychnine-like alkaloids exert their action early, and the morphine-like substances take effect later (2).

Credit for the establishment of the chemical structures and synthesis of most of the alkaloids found in peyote goes to Späth (7,8,9). Slotta and Heller (10) and Slotta and Szyszka (11) devised a more practical method of synthesis starting with gallic acid and including electrolytic reduction of the nitro-styrol. In 1951 Tsao (12) and Benington and Morin(13) reported on methods starting with gallic acid using lithium aluminum hydride as a reducing agent.

TABLE I

ALKALOIDS OF PEYOTE

NAME	FORMULA	STRUCTURAL FORMULA	%	DISCOVERED SYNTHESIZED
Mescaline	$C_{11}H_{17}O_3N$		0.9	Heffter 1896 Heffter & Capellman 1905; Späth 1920.
Anhaline (Hordenine)	$C_{10}H_{15}ON$		0.25	Heffter 1894; Späth 1920.
Anhalonidine	$C_{12}H_{17}O_3N$		0.25	Heffter 1896; Späth 1922.
Pellotine	$C_{13}H_{19}O_3N$		0.20	Heffter 1894; Späth 1922.
Anhalamine	$C_{11}H_{15}O_3N$		0.1	Käuder 1899; Späth 1921.
Anhalonine	$C_{12}H_{15}O_3N$		0.01	Heffter 1896
Anhalidine	$C_{12}H_{17}O_3N$	N-Methyl Anhalamine	0.001	
Anhalinine	$C_{12}H_{17}O_3N$	O-Methyl Anhalamine	little	
Lophophorine	$C_{13}H_{17}O_3N$		little	Heffter 1896.

ASSAY:

Slotta and Müller (14) reported finding trimethoxyphenylacetic acid in the urine of rabbits and a dog fed mescaline. Richter (15) reported on a method for the determination of amines in human urine. He reported that mescaline was excreted rapidly and unchanged. Dessi and Rizzoli (16) improved the colorimetric method of Richter so it could be used for determinations with blood as well as urine. Munier and Macheboef (17) found that it was practical to separate alkaloids using microchromatography. With their method they could detect less than 10 micrograms. Dessi (18) reported on a further improvement of Richter's method in 1950. In 1951 a group from Seevers laboratory described a colorimetric method using bromcresol purple (19). This appears to be one of the best methods to date and can be used for determinations on extracts from plasma, whole blood, urine, and tissue. Block (20) using C_{14} labeled mescaline was able to detect it on paper chromatograms after hydrolyzing tissue homogenates.

DISTRIBUTION:

Considering the interest which has been shown in mescaline, relatively little is known about its distribution and excretion. This has been due to the lack of sensitivity in earlier methods. Möller (21) reported that he could recover ninety-four per cent of the administered drug from urine of normal subjects, but the recovery in psychopathic patients was considerably lower. No free mescaline was detected in the twenty-four hour urine of dogs fed large doses by Slotta and Müller (14); however, they isolated

40-50 per cent of the administered amine as the 3,4,5--trimethoxyphenylacetic acid and found some of the free amine in the feces. These same investigators were not able to discover either the free amine or the acid in human urine after ingestion of 400 mgm of mescaline. Using a microcolorimetric process, Richter (15) recovered from the urine 53 per cent of an intravenous dose and 58 per cent of an oral dose of mescaline given to human beings. Salomon (22) using a method based on determination of methoxy groups found 9-39 per cent of the ingested mescaline excreted in eighteen hours with a peak excretion at six hours. He found no difference in excretion rates between normal and abnormal subjects. The group at Seevers (23) laboratory studied the plasma levels, excretion, and distribution in tissues from dogs with their methods. They found that plasma levels reached a peak immediately after intravenous administration. The peak after intramuscular and oral administration was reached more slowly. The plasma concentrations after all routes of administration remained relatively constant for two to four hours and detectable amounts could still be found after ten hours had elapsed. No apparent difference in the amount of mescaline recovered from the urine was found regardless of the route of administration. A range of 28-46 per cent of the dose was recovered from the urine of dogs. This is the same range reported by investigators at the Lexington, Ky. hospital for narcotic addiction (23) in results obtained with human beings. Block (107) reported that he found 79.4 per cent of the fed dose of mescaline as mescaline, and 16.2 per cent trimethoxyphenylacetic acid in the urine of white mice. The values for rat urine were 18.4 per cent as mescaline and 72.4 per cent as trimethoxyphenylacetic acid.

Tissue distribution studies showed a selective deposition in the parenchymatous organs studied; liver, spleen, and kidney. The concentrations in these organs at one hour were three to six times those in the plasma. After three hours there was a noticeable decrease in the liver and the spleen which was probably due to the fact that this is the period of peak excretion. The concentrations in the brain and blood were of the same order of magnitude which confirmed the work of Vogt (24). The latter investigator did not find differences in concentration between occipital and frontal cortex of monkeys. The erythrocyte-plasma ratio has been found to be 1.2-1.4 to 1. There was also a high concentration in ventricular muscle at the end of one hour which had dropped to the plasma level at the end of three hours. Using mescaline labeled with a C_{14} atom adjacent to the nitrogen atom, Block (107,20) found he could chromatograph the actual amine from protein hydrolysates with the following results given in counts per 10 mgm dried tissue: heart 13, spleen 10, liver 8, brain 7, kidney 6, muscle 6, lung 4.5, testes 4, and thyroid 2.6 (20). These observations were made on tissues taken six hours after administration of the drug to mice. He concluded from his results that mescaline was not adsorbed to proteins but was actually enzymatically incorporated into proteins by the liver. Block (108) concluded in his most recent paper that mescaline is incorporated into proteins by some mechanism which is different from that involved in the incorporation of amino acids into proteins.

At present it is not known in what form mescaline is excreted by human beings. All determinations to date have indicated a marked discrepancy between the amount of mescaline ingested and the amount excreted. It may be that mescaline is partially excreted in some form not detectable by present methods or that a portion of the dose enters a metabolic pool. The distribution of mescaline in the human being is also unknown. It appears from animal experiments that the greatest deposition is in the parenchymatous organs while concentrations in the brain are relatively low.

ENZYMATIC REACTIONS:

Since mescaline apparently has many effects similar to epinephrine, it seemed reasonable to suspect that its action might be due to interference with the destruction of epinephrine such as has been suggested for the mechanism of action of ephedrine. Woods et al (19) felt that the chemical constitution of mescaline would indicate three possible alterations of the drug within the animal body. Thus, demethylation or oxidation to form a phenol, oxidative deamination of the amino group, or methylation of the amino group must be considered as possibilities. However, they found no evidence of N-methylation to any significant degree. Although they were not able to confirm the results of Slotta and Müller, they were not willing to exclude oxidative deamination to 3,4,5-trimethoxyphenyl acid as a major path in the metabolism of mescaline (19). Bernheim and Bernheim (25) studied the oxidation of amines by amine oxidase in vitro. They found that the presence of the trimethoxy groups had a profound effect on the activity of the enzyme and concluded that while mescaline is oxidized in the rabbit, it is very slowly oxidized by this enzyme in other animals. They found that the affinity constant of tyramine for amine oxidase was 2.5×10^{-3} while that for mescaline was $.25 \times 10^{-3}$ in the rabbit. From this they concluded that the action of mescaline could not be explained on the basis of a greater affinity of the substance for amine oxidase (25).

TABLE II

RATE OF OXIDATION OF MESCALINE

ANIMAL	LIVER	KIDNEY
Rabbit	2	1
Rat	1	0
Guinea Pig	1	0
Cat	0	0
Dog	0	0

LEGEND

2= readily oxidized
1=slowly oxidized
0=not oxidized

The results of Berhheim and Bernheim confirmed the work of Pugh and Quastel (26) who also found that mescaline was attacked feebly or not at all by amine oxidase. Alles and Heegaard (27) included mescaline in their studies on substrate specificity of amine oxidase and found that mescaline was not oxidized at all under the conditions of their experiments as compared with the 100 per cent oxidation of phenyethylamine. Blaschko (28) also concluded that mescaline probably is not oxidized by amine oxidase except in the rabbit liver. He suggested that this is the reason for the rabbits high tolerance of mescaline. Slotta and Müller (14) had reported that the rabbit had a tolerance seventy times that of man on a weight basis.

More recent work by Block (101) showed that the alleged in vitro incorporation of C_{14} mescaline into proteins depends on the presence of oxygen and that the pH, time, and substrate dependence curves indicate that an enzymatic reaction is involved. The addition of tyramine or heating to 50-55° C increased the rate of incorporation. From this work he concluded that there was an inhibiting substance, possibly amine oxidase, for which tyramine had great affinity. When the action of this substance was blocked by competitive inhibition, the incorporation of other amines into proteins was facilitated. Further work by Block (102), however, demonstrated that the inhibiting agent was not amine oxidase since a number of known amine oxidase inhibitors do not produce an increase in mescaline incorporation. He concluded that there was a small quantity of mescaline oxidase present in mouse, rat and cattle.

It appears from all the evidence that the action of mescaline cannot be attributed solely to interference with amine oxidase activity. Ahlquist (29) in his chapter on adrenergic drugs in "Pharmacology in Medicine" pointed out that the theory that ephedrine acts only by inhibition of the destruction of epinephrine by amine oxidase has been questioned.

Hoffer, Osmond, and Smythies (30) have still another theory. They suggest that mescaline may be able to close its side chain to form an indole ring. This was a good possibility as it had been reported that mescaline can condense readily with an aldehyde to form a secondary amine (1). In this way a compound would be formed that would resemble the naturally occurring adrenochrome, a product of oxidation of epinephrine by the phenolase system. Woods et al (19) from a consideration of the chemical formula of mescaline suggested that demethylation of the methoxy groups may take place, but to date there is no experimental evidence that it does occur. The methyl groups can be hydrolyzed to OH groups with HCl at 130-150° F yielding trihydroxyphenylethylamine which condenses at 37°C and standard atmospheric pressure with pyruvic acid (1). Salomon, (22), however, used the trimethoxy groups excreted in urine as an index of excretion of mescaline. There does not appear to be any conclusive evidence at this time that mescaline is either demethylated or changed into an indole derivative, but both reactions are possible and both could have an effect on the oxidation of epinephrine by the phenolase system. An interesting observation of Friedenwald and Herrmann (31) that not only did quinones apparently inactivate sulfhydryl groups in enzymes, but it appeared possible that the oxidation of adrenaline by the cytochrome oxidase system or by polyphenoloxidase results in the production of substances capable of inhibiting amine oxidase. They found that the inhibiting agent was not adrenochrome but some unstable precursor. Another avenue for speculation is opened concerning the possibility that mescaline acts by preventing the further oxidation of adrenochrome, thus permitting an increase in the concentration of the quinone in the circulation.

Information concerning the action of mescaline on other enzyme systems is still more scarce. Pugh and Quastel (26) reported that mescaline inhibited O_2 uptake by brain cortex slices in a glucose containing medium. Synergism between thiamine and dl-benzedrine, tyramine, and mescaline was demonstrated by Dessi and Labo (32). They found that in mice and rats the giving of thiamine with these drugs caused death where the drug alone had not been lethal. The animals appeared to die from toxic dose of thiamine rather than the arylalkylamine. Further research on the effect of mescaline, lysergic acid, and related drugs on respiratory enzymes of the brain was pursued by Clark, Fox, Benington, and Morin (33). These investigators found that while amphetamine increased succinic dehydrogenase activity, lysergic acid had no effect, lysergic acid diethylamide was moderately inhibitory, and mescaline had almost no effect. Amphetamine and the amide of lysergic acid strongly stimulated the cytochrome oxidase system while the free acid and mescaline had no effect. Mescaline was found to decrease the oxidation of pyruvic acid in brain homogenate. It was found by Lewis and McIlwain (34) that dihydroergotamine, lysergic acid diethylamide, mescaline sulfate, and dibenamine had no effect on the metabolism of guinea pig cortical slices in vitro normally, but had an inhibitory effect after the tissue had been stimulated. The fact that mescaline had little effect in vitro on succinic dehydrogenase would suggest that it does not act by inactivating sulfhydryl enzymes, however, this does not exclude the possibility that this reaction can take place in vivo. Delay, Gerard, and Thullier (35) found sodium succinate had some effect in protecting mice against a lethal dose of mescaline. Certainly the inhibition of carbohydrate metabolism points to some interference with the Krebs cycle. Ellis (78) demonstrated that mescaline competed for liver receptors for epinephrine thus preventing hyperglycemia. Apparently there is good basis for the feeling that mescaline has some effect on the energy metabolism of the organism, but the exact mechanism remains obscure.

ACUTE TOXICITY:

No human being has died as a result of taking either peyote or synthetic mescaline in doses ranging up to 750 mgm taken orally. Up to 600 mgm have been given to human beings intravenously without causing death. There never has been an admittance to the Lexington Hospital for addiction to mescaline, and Seevers (29,19/14) reported that dogs fed 5gm/kgm body weight of ground peyote daily for twelve months showed only a tolerance to the emetic effects. He stated, "In the absence of clearly defined emotional dependence or of significant harm to the individual or society, there exists no possible basis for categorizing peyote as an addicting drug." Mayer-Gross (38) reported that nitrogen retention occurred when dogs were fed mescaline, and massive excretion occurred when the drug was withdrawn. Capillary damage in the liver was his pathological finding. Rabbits, on the other hand, tolerate 800 mgm mescaline sulfate which on a weight basis is seventy times the dose tolerated by man (14).

Dogs injected with 1cc/kgm body weight of the pan-peyotl extract died in convulsions, whereas, it took 2 cc/kgm to kill a rabbit (2). The LD50 of mescaline sulfate was found to be 17.8 mgm/100 gm intravenously, and 50 mgm/100 gm intraperitoneally for white mice (37) Grace (43) found the LD50 for white mice to be 50-60 mgm/100 gm intraperitoneally, and 50 mgm/100 gm hypodermically for guinea pigs. Simple calculation shows that a similar dose on a weight basis for a 70 kgm man would amount to 25.9 gm of the pure alkaloid. Therefore, the lethal dose given in the literature for animals is so far in excess of any dose ever taken by man that one has no way of judging how this may relate to man.

Wikler (37) reported in the discussion of Hoch's paper that 5-6 mgm/kgm body weight of mescaline sulfate given orally was optimal for the hallucinogenic effect while doses larger than this produce unpleasant sympathomimetic side effects. At one time 146 average sized dried peyote buttons were weighed, and their weight was found to be approximately 1.5 gm per button. LaBarre (2) stated that from four to forty buttons are eaten at a ceremony. If one calculated the content of mescaline on the basis of Späth's figures at 0.9 per cent, one may conclude that the Indians usually consume something on the order of 0.054--0.540 gm of the alkaloid during the night, which is about optimal for the visual effects without too many unpleasant side reactions.

PHYSIOLOGICAL REACTIONS:

Cardiovascular

LaBarre listed considerable data concerning physiological reactions of pan-peyotl (2). Since this is a mixture of both morphine-like and strychnine-like substances which produce a mixture of effects, the discussion will be limited to the reactions of synthetic mescaline.

In human beings a small rise of blood pressure with increased force of heart beat was reported by Stockings (39). A rise in blood pressure of 10-20 mm Hg was also found by Guttmann (40). It was not stated whether this was systolic, diastolic, or both. This investigator also found a fast pulse which was contradictory to the findings of Stockings who reported that an initial acceleration was followed by slowing. Rouhier (41) also found a slowed pulse with mescaline, and slowing of the heart rate was described by Hamet (42). Hamet found mescaline to cause a pressor response in the decapitated cat (43). This pressor effect was not blocked when the ganglia were paralyzed with nicotine.

Hamet (42) found that the slowing of the heart rate was not blocked with atropine in chloralosed dogs. This is also the finding of a number of other investigators using frogs. Grace (43) reported that the slowing in the perfused rabbit and frog heart was not blocked by atropine and that the heart stopped in diastole. He attributed the slowing to lengthening of diastolic pause. He also observed that if at any time before the heart stopped the drug was replaced with Ringer's solution, the heart would rapidly recover. A record taken of the coronary flow showed no action on these vessels.

Cochin, et al (23) reported that during the first hour the concentration of mescaline in ventricular muscle was high in comparison to its concentration in plasma. The marked slowing of the pulse was one of the most consistently reported physiological effects of mescaline, and it would appear from the discussion above that toxicity to the heart should be considered when mescaline is used experimentally.

Respiration

The effect of mescaline on the respiration appeared to be variable. No alteration was found by Guttmann (40), although, he does report that one person out of sixty developed Cheyne-Stokes respiration while two hyperventilated. Stockings (39), on the other hand, felt that mescaline was a powerful medullary stimulant which produced hyperpnea and eventually Cheyne-Stokes respiration. Some observers reported shallower and more rapid breathing with occasional long drawn out sighs and a painful feeling of suffocation (2). Experiments with anesthetized dogs, cats, rabbits, and frogs have all resulted in respiratory inhibition. Grace (43) found that respiratory inhibition could be blocked by either atropine or cutting the vagi. The same results were found by this investigator using decerebrate cats. Arrest of respiration and asphyxial convulsions were consistently given as a cause of death in the dog, cat, frog, rabbit, and guinea pig. From this Grace (43) concluded that in both frogs and mammals the main effect of mescaline is depression of the central nervous system.

Skeletal Muscle

Peyote was formerly used by the Indians to reduce fatigue during races, fighting, and on long journeys (2). Stockings (39) reported that he found no muscular weakness or rigidity in man, but that there was a mild degree of tremor and incoordination. Tremor and incoordination were also found by Hoch(37). A sensation of heaviness of the limbs and a disinclination to move was frequently reported by people who have taken either peyote or mescaline (2). Lindemann (44) did not find a marked change in chronaxie. Klüver (45) found that although he had no desire to move about that he could perform gymnastic exercises when asked to do so without a sense of fatigue. Few experiments have been done to study the effect of mescaline on skeletal muscle. However, Grace (43) found that mescaline in any concentration over 1:500 shortened the isolated gastrocnemius muscle of the frog while the individual contractions diminished as the result of restricted relaxation. The antifatiguing action of mescaline in low doses may be related to the well known anticurare effect of epinephrine.

Gastrointestinal System, Smooth Muscle

Effects on the gastrointestinal system have rarely been reported. The most commonly recognized action is the feeling of fullness and nausea. LaBarre (2) alleged that this was apparently of central origin as it was produced even when the alkaloid was injected intravenously. However, since injected drugs will be present in the circulation of the gastrointestinal system, a direct effect can not be ruled out. The experiments on isolated tissues which are described as follows are better evidence for a central action.

Grace (43) is to be credited with the few experiments which have been done on animals. He used the isolated duodenum of rabbits and cats and the isolated pregnant and non-pregnant uteri of cat, rabbit, guinea pig, and rat. No effects were found with mescaline on any of these preparations with any concentration. However, when mescaline was tried on intact intestine and uteri in these animals, the drug caused powerful contractions after intravenous injection. The contractions were blocked with atropine. The immediate tonic contraction of the non-pregnant uterus did not abolish the rhythmic contractions. The effect was also found with the decapitated cat and was not abolished by previously paralyzing the ganglia with nicotine (43). Raymond Hamet found that medium doses of mescaline produced a marked stimulation of intestinal movements in situ, followed by a lowered tonus, which is an effect similar to that of nicotine (42).

Liver, Kidney, and Spleen

Mayer Gross' finding of capillary damage in the livers of dogs fed mescaline is one of the rare references to effects on the liver (38). The possibility that mescaline is detoxified by liver enzymes and the results of Block (20), which indicate that mescaline may be incorporated into proteins in the liver, point to this organ as being of importance in the metabolism of mescaline. The finding of Cochin et al (23) of a high concentration in the livers of dogs was further evidence that the liver plays a role in the detoxification process. Sloane and Doust found that mescaline decreased hippuric acid excretion (46). Certainly, the possibility that deficient liver function might increase the toxicity of mescaline should be considered when using the drug experimentally.

Still less is reported for kidney and spleen. Stockings reported that urine was scant and dark colored (39). This was also found by Slotta and Müller (14). Salomon et al state that the initial suppression of urine is compensated for by greater flow later (22). There have been many reports in the literature that pan-peyotl has a diuretic action (2). Again, Cochin et al, Vogt, and Block have all reported high values for mescaline in the kidneys as compared with plasma indicating that mescaline or its by-products were excreted by the kidney. In an experiment in which four people took either peyote or mescaline, the urine was reduced in volume, contained no glucose or acetone bodies, and was cloudy. Dark colored urine was observed one day after ingestion of the drugs (103). The nature of the substance producing the color should be investigated as it could either be an oxidation product of the amine or a product of hemolysis. High concentrations of mescaline were found by Seever's group in the spleens of dogs (19).

Nervous System

By far the most striking effects of mescaline were produced on the nervous system. The well known and most studied phenomena of production of color visions appear to be related in some way to possible toxic psychoses or hypnotic hallucinations and may indicate some effect on the occipital cortex or temporal lobe function. Experiencing these visions is the goal of the Indians who take peyote in their ceremonies, particularly among those people who have the pattern of a vision quest in their culture (2). The hallucinations are vivid in color, appear to be real, although the person is aware that they are not real, usually involve motion, and the colors have a prismatic quality. The visions may take the form of scenes, people, or objects, and may be distorted in size or they may be of abstract designs of moving wheels, spots, or geometrical figures. Synesthesias of hearing, or kinesthetic sense may accompany the visual experience (45). It is well agreed that the content of the visions is dependent upon the psychological background of the individual and that they can not be modified by will or suggestion. The visions may be seen to advantage with the eyes shut and have been reported in studies on people who were blind due to a variety of causes (47). The response of a person to mescaline intoxication can to some extent be predicted from the Rorschach test (37,40).

According to Guttmann (40) color is intensified, after image increased in duration, and the hallucinations are more distinct in a dark room than a lighted one. In addition, perception of space is altered. Mydriasis persists for several hours and the hallucinations can sometimes be invoked by pressure on the eyeballs. Marinesco(48) described the experiences of two artists who took mescaline and attempted to reproduce their images in color. These people found the hallucinations agreeable, their affectivity was increased, and although critical power was reduced, they never believed in the reality of their visions. Morselli (36) gave a resume of his personal experience in great detail. Although the toxic symptoms lasted about sixteen hours, he felt a certain mild hallucination persisted for about two months; ie, the occasional feeling that a portrait hanging in his room had a live quality. Psychotic manifestations which lasted ten to twelve hours were described by Hoch (37) and were found to be present in a clear state of consciousness. He felt that they emphasized schizoid tendencies in borderline cases but felt that he had insufficient material to warrant using mescaline for differential diagnosis. He also found that mescaline could reactivate psychotic behavior which had been eliminated after psychosurgery. The psychotic state was not affected by suggestion, hypnosis was difficult, and electroschock had no effect on it. Salomon et al (22) found that there was actually a decrease in perception of color as determined by flicker fusion thresholds. There was some correlation with the size of dose and vividness of hallucinations and also with the excretion of methoxyl groups. On the other hand, color perception especially for lighthouse red and nile green was more impaired by small doses than large ones. They concluded that vividness of hallucinations was definitely not associated with impairment of color perception.

Klüver (45) investigated mescal visions and their relation to eidetic imagery using himself as a subject. His conclusions were as follows: with regard to color vision there was a general increase in brightness which was most noticeable in the peripheral region; in foveal vision objects seemed to become loose and cloudy; and movements of objects were frequently observed. After images appeared vivid and at one time the after image of the right hand seemed equally as real to him as the hand he knew he was holding under the table. Karwoski (49) could determine no clearcut effect of mescaline on thresholds to light and color. Stockings (39) said the retinal cells were affected causing exaggeration of after image. Mydriasis is reported by all investigators with both human beings and animals. The Indians feel that this makes a hunter see better and nocturnal animals like the skunk were chosen as totems because of their supposedly superior eyesight (2). Present day peyote cult members suffer from photophobia the following day and wear sunglasses to relieve the condition(2). Grace (43) found that mescaline did not cause mydriasis when placed in the eye of an animal. Thus, dilatation of the pupil seems to be of central origin. Although retinal cells may be involved in the production of more intense after images, the visual hallucinations appear to be of central origin since they can be elicited in the blind. The finding that the visions can be invoked best with the eyes closed is consistent with this idea.

In reference to other senses Uchida (50) found generally a hypersensitivity of all senses with the exception of gustation. He (51) also mentioned a definite decrease in mental work, intense perseveration, overestimation of time, and irregularity of reaction times. Uchida (52) felt that there was a certain symptomatic resemblance between mescaline intoxicated subjects and schizoid individuals in regards to catalepsy, apraxia, suggestibility, stereotypy, and other catatonic symptoms. Klüver (45) found the tones of his violin to be more voluminous and even sounds like swallowing were unusually loud. Papp (53) found that posthypnotic suggestions were modified becoming more vivid and being completed by symbolic elements. Stockings (39) mentioned a dulling of pain sense and loss of thermal appreciation. Mayer-Gross (38) said that the change in tactile sensation was due to an alteration of the normal process of fatigue, and of recovery of sense organs. Lindemann (44) was not able to find much change in reflex time. An interesting observation of Zador (54) was that the phantom limb was more affected by mescaline than other parts of the body. The feeling of nausea which was present with the drug in the early stage of intoxication, the feeling of fullness associated with anorexia, and the distortion of time, were further alterations of sensation which were universally reported.

In regard to behavior in general there have been numerous studies using the Rorschach test (40). From these studies some investigators have concluded that different personality types reacted to mescaline in different ways and that the outcome of the drug intoxication could be predicted from the test. Hoch (37) felt that there was no change to another type, but, rather, that there was an underscoring of the personality. Lindemann (44) stated:

> "On the one hand, we have observed in certain patients withdrawal of interest from the outside world and regression to more primitive types of mental behavior from a previous level which was in closer coherence with environmental demands. On the other hand, we found a simultaneous transformation of neurophysiological patterns resulting in loss of the normal level of responsiveness and of the normal pattern of co-ordination which was established as most suitable to meet the environmental demands placed upon the motor system. Here, the same as there, we have a regression to a more primitive, less adequate level of behavior. A drug which restores outside contact also restores the normal level of co-ordination. A drug which facilitates withdrawal from the outside also produces a regression of neurophysiological responsiveness."

In a comparison of the effect of sodium amytal, cocaine, hashish, and mescaline, Lindemann and Malamud (55) found the following: normal people experience changes in perception, become emotionally distant, and self-absorbed; psychoneurotics had a pronounced fear of and resistance against changes in reality; while schizophrenics had a tendency to catatonia, increased hallucinatory experiences, and elaboration of these in relation to the psychosis under the influence of mescaline. Osmond and Smythies (56) in one of their papers compared the remarkable similarity between the symptoms of acute schizophrenia and mescaline intoxication. Catatonia was the common finding among animals. Cattell (57) studied the influence of mescaline on psychodynamic material and found less inhibition. The pseudoneurotic group was most accessible while less accessible groups were not helped. Spindler (58) found the peyote cult members of the Menomini tribe to be psychological and sociological deviants on the basis of Rorshach tests. One interesting study was made on the effect of mescaline on a conditioned reflex in animals (59). In this experiment normally a buzzer caused the animal to move into another compartment while one and a half hours after the injection with mescaline, the animal would only jump and squeal as though it had been shocked at the sound of the buzzer. There are several mentions of the effect of mescaline on the electroencephalogram of human beings. Reduction in alpha activity and low voltage fast activity were the common findings. These changes were not related to tremor or to the hallucination (37, 60).

In general it is agreed that the effects of mescaline intoxication resemble in many respects the symptoms of schizophrenia. There have been many explanations as to how this effect comes about. One of the older theories is that the inhibition of mescaline on the respiration of the brain plays a part (26). Another theory pursued extensively is that mescaline interfers with epinephrine metabolism possibly by blocking the action of amine oxidase. Other investigators have felt that mescaline is not the substance actually involved but that a product of oxidation, possibly an aldehyde, is the agent.

Marazzi (61) found that mescaline, epinephrine, and amphetamine all inhibited central nervous system synapses. This effect was also found by him at all levels of the nervous system. Grace (43) and Hamet (42) did not feel that mescaline was a true sympathomimetic drug. Experiments with electroshock showed that mescaline and cocaine raised the threshold instead of decreasing it like other central stimulating drugs. This effect was interpreted by Tainter (62) as a possible inhibition of suppressor circuits. This possible predilection for certain pathways was brought to attention also by Klüver's finding of uncinate fits in monkeys and by the observation of Cochin (23) et al, of peculiar chewing movements in the dog. Osmond and Smythies (64) have an interesting theory which is based on the chemical resemblance of mescaline to norepinephrine and epinephrine from which they postulate the possibility that adrenochrome or a substance similar may be a cause of the schizophrenic state.

Still another theory proposes that mescaline and lysergic acid amide may be serotonin antimetabolites (65). Gellhorn (66/145) reported that anti-cholinesterases increase convulsant action of mescaline which suggests the involvement of the acetylcholine functions. Fischer (67), on the other hand, said all hallucinogens have adrenergic blocking activity which results in sympathetic hypertonus followed by blockade. Block (68) et al, described their findings in relation to the incorporation of mescaline into liver proteins and suggested that the neurovegative reactions which occurred in the early stages were the result of mescaline action directly and that the psychotic manifestations may be related to the presence of a foreign amine-protein compound. Goodman and Gilman (69) at one time classified mescaline with miscellaneous cardiovascular drugs. Mescaline has been classified as a central depressant by Hamet and Grace, as a true cortical stimulant by Hoch, and as a powerful stimulant of medullary centers by Stockings. Bridger and Gannt (104) studied the effect of mescaline on conditioned reflexes in dogs. They found that the dogs reacted to the conditioning stimulus as though it were the unconditioning stimulus; in their words, the signal for reality became reality itself. From these experiments they concluded that mescaline produced an inhibition and cleavage of normally coordinated systems of higher nervous activity.

Certainly the theories concerning the mechanism of action of mescaline are as varied as the theories concerning the etiology of behavior disorder. There is, however, one point in common in all of these theories, namely, the involvement of the autonomic nervous system and more specifically of epinephrine. It should be emphasized that although mescaline intoxication has been compared by many investigators to the symotoms of acute schizophrenia, these states are not identical. In mescaline intoxication the individual does not lose contact with the environment. The symptoms suggest that there is a disturbance of occipital and temporal lobe function.

METHODS

Rats were chosen as the experimental animals not only because of their convenience but also because their ability to metabolize mescaline somewhat matched that of human beings (25). Only males approximately four months old of an inbred strain of Sprague-Dawley white rats were used. This strain has been inbred for at least three years in the rat colony of the Anatomy Department of the University of Colorado School of Medicine. These animals are noted for being remarkably uniform; they are free from tumors and infection and are easily handled. The size was kept between 160-200 gm. Unless otherwise specified, the rats had been allowed to feed ad lib up to the time of the experiment.

It was necessary to devise a method for doing electroencephalograms (EEG's) on rats. This took considerable time since it was also necessary to work out standards for comparison. Phonograph needle electrodes were used. Care was taken to choose a brand of needle which had a short stylus so that the brain would not be pierced too deeply. Soldering the wire close to the stylus cut down considerably the artifact due to wire wave and leverage. It was planned originally to use pentobarbital anesthesia, but it soon developed that mescaline had a slight but definite analeptic action. The excitement of the animal as it came out from anesthesia usually caused the electrodes to be pulled out. Local procaine anesthesia appeared to be sufficient for the insertion of the electrodes and did not produce excitement as its effects wore off. Upon recovery from the procaine a waking normal record could be taken.

Any form of restraint resulted in low voltage fast activity in the EEG record. It was suggested that, since immobilizing rats by putting the animal in a child's sock with its head sticking out of a hole in the toe did not result in any change in thyroid activity and did not appear to be a stressing type of restraint, this might be an acceptable method for our purposes (105). It was also known that rats conditioned to an apparatus showed no change in cholesterol and ascorbic acid levels (70). Consequently, a combination of conditioning the animals by handling and petting, a quiet laboratory, and immobilization in a sock, was settled upon as the procedure of choice. With this procedure and much patience it was even possible to record the EEG of a sleeping rat.

Originally, four electrodes were placed in the skull of the rat; the frontal pair in a line with the outer corner of the animal's eyes and the occipital pair on a level with the external auditory meatus. These four electrodes made a square of approximately one centimeter on a side. As a reference lead a fifth electrode was added posterior to the ears over the cerebellum. It was found that piercing the brain did not produce spikes. It, therefore, appeared feasible to insert the electrodes carefully with a slightly slanting thrust to avoid breaking the skull. The exact position of the electrodes was then checked at autopsy. It was found that rats under two hundred grams of weight had more cartilaginous skulls than older rats. There was not only less damage to the skull in the younger rats, but the electrodes were held more firmly in place.

The tips of the frontal electrodes were invariably in the corpus callosum over the caudate nucleus. The position of the occipital electrodes was more variable. An attempt was made to place them in the posterior thalamic nucleus between the corpora quadrigemini and the hippocampus (71,72). The electrodes were always below the level of the corpus callosum. It was found that when the electrode was inadvertantly placed a little more laterally and anteriorly that it was in the hippocampus and the record was apt to show focal spike activity. It was felt that the use of a steriotaxic apparatus would improve the technique, but such an instrument was not available at the time. The electrodes did not appear to bother the animals after the procaine wore off. The rats survived indefinitely at the conclusion of the experiment.

The recording instrument was a Grass eight channel electroencephalograph. The first four channels were occupied by the recordings from the four electrodes to the common lead over the cerebellum. The next two channels were used for bipolar recordings of the anterior and posterior pairs of electrodes. This is the activity described in this work. The seventh channel was used for a simultaneous recording of the respiration using a pneumograph and a bonded Statham .2 psi strain gauge. The eighth channel was reserved for recording the electrocardiogram using a combination of the right frontal electrode and an additional electrode inserted in the tail. The apparatus and the rat were in a screen cage which was grounded to the instrument.

For the most part the standard EEG filter, regular paper speed, and an amplification at which fifty microvolts caused a 3 mm deflection of the pen was used. Since the different activities were brought out at different amplifications, the procedure of making some of the recording at such an amplification that fifty microvolts produced a deflection of 5 mm was adopted. This was the highest amplification which could be used on records from normal rats without causing a squaring of the highest waves. A portion of each record was made using the EMG filter to screen out slow activity, at twice the regular speed, and at the higher amplification so that the character of the low voltage fast activity could be examined. A record of sleep or drowsy activity was attempted with each rat if time permitted. During this record the room was quiet, darkened, and the rat was gently petted. Arousal was relatively easy to record following the drowsy record by alerting the animal with a sudden noise.

The EEG record was analyzed by visual inspection. Representative portions of the recording were chosen. Spikes were not counted as waves but were described. Waves faster than fifteen per second and lower than twenty microvolts were considered as low voltage fast activity. These waves were counted in the speeded up portion of the record. The per cent of time that each activity was present was calculated and expressed as percentage time duration. A frequency spectrum of each experimental group was made on the basis of per cent of waves counted excluding the low voltage fast activity. Finally, the frequencies were grouped not only because they fell within the standard alpha, beta, and delta ranges, but because the distribution seemed to indicate peaks within those ranges. The groupings decided upon were 1-4, 5-8, 9-14, and low voltage fast activity. The waves were measured with the help of a transparent gauge. Every effort was made to avoid calling the higher frequencies multiples of the slower ones by checking and re-checking with different combinations of the analyzer. It was realized that there are many inadequacies in such a method, but it was kept as consistent as possible. It appears to be a practical method for dealing with EEG's of rats under normal laboratory conditions.

Normal cortical activity was recorded after the animal had recovered from the anesthesia. If time permitted and the animal appeared drowsy, a sleep record was attempted. The drugs were given intraperitoneally or subcutaneously as indicated. The recording was continued for at least an hour after injection. The recordings were not continuous, but samples were taken at five minute intervals of at least two minutes duration. If for any reason, such as signs of a convulsion, it appeared to record the activity at other times, it was done.

Blood sugars were determined by the Nelson variation of the Somogyi method. The blood was taken from the tip of the tail during the control record, and at a half hour, and one hour after the injection of the drug.

Pain was checked both by the reaction to the tail snipping procedure at the time blood samples were taken, and by pin prick during the course of the record. Corneal reflex, spinal reflex, and righting reflex were checked periodically. Arousal and reaction to key jangling were checked during the control period and at an hour after injection of the drug. Observations were also made on the warmth and color of the tail as an indication of vasoconstriction. Color of the ears, nose, and feet was checked for cyanosis. The degree of salivation, condition of the conjunctiva, tremor, nibbling, and licking were all observed and recorded. The behavior of the rats was observed during the recording and after the animal was returned to his cage with respect both to his individual behavior and in relation to other animals.

The chronic experiment was maintained for a month and a half. The group of ten control rats was given injections of half a cc of Ringer's solution per hundred grams of body weight. The experimentals were given 5 mgm per hundred grams of body weight of the synthetic mescaline sulfate. The injections were given daily for five days of the week. Weights were checked weekly. Daily observations were made concerning irritability and appearance. Threshold to electroshock was checked before the experiment started and at its conclusion one half hour after the daily dose of mescaline had been given. At the end of the experiment EEG's were recorded on both the controls and the mescaline injected rats in the usual manner. Both pre-injection and post-injection blood sugar levels were determined at this time.

Threshold to electroshock was determined by the method described by Tainter (62). It was necessary to adapt this method for use with the Hans stimulator. Thus, a time duration of half a second was used instead of several seconds. A pre-threshold level resulted in very marked hyperactivity while a true threshold shock produced a tonic-clonic type of convulsion followed by a prolonged period of confusion and catatonic behavior. The thresholds were determined as the number of milliamperes necessary to produce the full convulsive sequence in 100 per cent of the rats of the group.

The blood for the studies on potassium and sodium levels was collected in a skin pocket after the axillary artery was cut under ether anesthesia. The tests were run using a Janke flame spectrometer with lithium as a standard. Temperatures were taken rectally. The one recording of blood pressure was made under pentobarbital anesthesia using a direct method. The LD50 was determined by probit analysis using the method of Litchfield and Wilcoxon (73).

The mescaline sulfate used was produced by Hoffmann-LaRoche.

RESULTS AND DISCUSSION

The resemblance of the chemical formula of mescaline to epinephrine and norepinephrine suggested the possibility that these substances have a similar mode of action.

The rat was chosen as the experimental animal not only because of its availability but because Bernheim's work on the oxidation of mescaline seemed to indicate that this animal resembled man in this respect(25). As it turned out, the rat proved convenient in other ways, as its blood sugar levels, ratio of serum sodium and potassium, and norepinephrine to epinephrine ratio is similar to that of man (74, 75). Only male rats were used since they are more sensitive to epinephrine than the female, and we wished to eliminate the effect of sex difference (76).

TOXICITY:

The first step was to determine the LD50 dose for adult, male, white rats which had not been fasted. Using the method of Litchfield and Wilcoxon, the LD50 was found to be an intraperitoneal dose of 37 mgm/100 gm of rat with upper and lower confidence limits of 41.0 mgm and 33.2 mgm respectively for 19/20 probability. Delay et al (35) gave 50 mgm/100 gm as an LD50 for intraperitoneal injection in white mice. These values are similar to those given by Grace (43) as follows: 75 mgm /100 gm hypodermically for frog, 50-60 mgm/ 100 gm intraperitoneally for white mouse, and 50 mgm/100 gm hypodermically for guinea pig. As time went on many factors were found to alter the toxicity of mescaline which will be discussed in succeeding paragraphs, however, no systematic investigation of the alteration of the LD50 was undertaken.

DOSE EFFECT:

The effects of increasing doses of mescaline were investigated. Again, adult, male rats were used which had been allowed food and water ad lib up until the time of the experiment. All rats had been brought to the laboratory several days in advance and handled frequently so that they would be accustomed to the electroencephalograph and other apparatus. At least six rats were used in all calculations involving blood sugar changes. Hemoconcentration was taken to mean a peripheral vasoconstriction which made blood difficult to take from the tail and which appeared to be associated with increased coagulability. The results are tabulated below; the symbols are to be interpreted as follows; + = moderate increase, ++ = considerable increase, +++ = great increase, - = moderate decrease, -- = considerable decrease.

TABLE III

EFFECTS OF VARIOUS DOSES OF MESCALINE SULFATE

Given as mgm/100 gm Body Weight I.P. to Adult, Male White Rats

EEG CHANGES:

Doses--	0	0.58	5.8	11.6	20.5	41.1
Bursts of spikes during hour before dose given.	4	2	2	9	0	0
Bursts of spikes during hour after dose given.	2	2	3	17	13	2
Random Spikiness	0	0	+	+	+	+
LVF-frequency	0	+	+	+	+	+
LVF-voltage	0	-	-	-	-	-

TABLE III
(continued)

EFFECTS OF VARIOUS DOSES OF MESCALINE SULFATE
Given as mgm/100 gm Body Weight I.P. to Adult, Male White Rats

Doses--	0	0.58	5.8	11.6	20.5	41.1
Deaths	0	0	0	2/14*	0	10/17**
Change in heart rate--½ hour	0	-16%	-29%	-37%***	-22%	-32%
Change in heart rate--1 hour	0	-3%	+4%	+7%	-4%	-5%
Blood glucose--1 hour	-2%	-2%	-48%	-64%	-66%	-72%
Temperature change--1 hour	+0.3°	-0.1°	+0.5°	+1.0°	+1.0°	+1.4°
Hemoconcentration--1 hour	0	0	++	+++	+	0
Catatonia--1 hour	0	0	0	0	++	0
Reaction to pain--1 hour	0	+++	-	--	-	-
Reaction to light touch--1 hour	0	+++	-	--	-	-

* Heart rupture after great acceleration.
** Respiratory failure.
*** This does not include two deaths.

The control rats were given intraperitoneal injections of distilled water which equalled in volume those doses containing mescaline. The size of the injection in this experiment was 1 cc/100 gm rat. All doses of mescaline over 70 mgm/100 gm resulted in the rapid death of the animal after a short period of hyperactivity. Violent flexor convulsions and cessation of respiration were the terminal events. Rarely was a transient extensor phase observed. The terminal convulsions were different from the spike discharges seen in the EEG, as the latter were not associated with any movement. It was not possible to block the terminal convulsions with curare or syncurine short of a lethal dose of these substances. Cyanosis, which was apparently associated with the period of maximal cardiac slowing, was always observed. At all doses, chewing, nibbling, sniffing, and sneezing were seen in the early stages of intoxication. There appeared to be a resemblance between the effects of mescaline and the dose effects given by Gellhorn for D.F.P.(66,p.147).

The EEG recordings were rarely continued beyond an hour, but in those few which were run for a longer time, there seemed to be a slowing in the record after three hours. The animals in general groomed themselves, huddled, or became catatonic; they were easily aroused and did not appear hungry when they were returned to their cages. Rarely did a rat become aggressive. When one did so, his cage mates became catatonic. All of the animals appeared more reactive to noises and blasts of air for several hours after the injection. Weakness of hind limbs, difficulty in crawling, trembling, and hyperactivity to a tap on the spine were generally noted. The following day the rats slept a great deal, and by the third day they had returned to normal behavior. It should be noted in TableIII that only the lowest dose is within the range of those taken by human beings, and for the most part those doses used in animal experiments by other investigators. From these results it appeared that there was a marked difference in the effects at different dose levels.

At low doses there was greatly increased reactivity to pain and touch, a change to low voltage fast activity in the EEG, a definite slowing of the heart, but no change in blood glucose. In moderately high doses depression of reaction to pain and light touch appeared. A maximum of heart slowing and hemoconcentration was reached. At high doses heart slowing and hemoconcentration decreased while death occurred due to respiratory arrest which was followed by cardiac arrest after some minutes. Electrical activity of the brain disappeared immediately after cessation of respiration. The drop in blood glucose after injection with mescaline was the only observation that seemed to increase consistently with the increase in dose. Blood sugar was still depressed at the end of four hours while the heart rate had returned to normal in an hour. From these data it appeared that the effects of increasing the dose of mescaline did not follow the usual logarithmic dose--effect relationship. At this time only speculations may be made concerning the probable action of mescaline.

1. Following the suggestions of Fischer (67) that an increase in circulating amines in addition to ganglionic blockade may be involved in the action of psychoses producing drugs, mescaline may act by progressively blocking receptors with different thresholds producing a progressive ganglionic blockade.

2. The relationship between increasing doses of mescaline and their effects suggest the type of curve found in enzyme-substrate

relationships. The possibility that mescaline may have some anticholinesterase activity which could result in increasing acetylcholine concentrations can not be excluded. The similarity between the effects of increasing mescaline doses and the effects found by Gellhorn (66, p. 145) for D.F.P., as well as his finding of synergism between anticholinesterases and mescaline, are suggestive that acetylcholine action is potentiated.

3. Mescaline may act by progressively blocking certain portions of the central nervous system such as the inhibitory and facilitatory reticular formations. Marrazzi (61) has found that mescaline and epinephrine inhibit central synapses. The work of Chatfield et al (90) suggests that some acetylcholine dependent systems in the cortex of the cat are more sensitive to blocking than others.

4. On the other hand, mescaline may act through a combination of these possibilities. On the peripheral side it may block receptors in the manner suggested by Ellis et al (78) whose work will be described later. In addition, the circulating mescaline and epinephrine may act by modifying synaptic transmission in the central nervous system which could result in a depression of first inhibitory and then of facilitatory systems.

FACTORS INFLUENCING THE ACTION OF MESCALINE:

The effect of twenty four hour fasting, insulin, and epinephrine, on the mescaline action was investigated. According to expectation it was found that a smaller dose of mescaline was necessary to cause a larger percentage decrease in blood sugar in the fasting animal. But, it was not expected that the percentage of decrease in glucose should fall off markedly in higher doses. Although the fasting level of glucose was lower to begin with, the drug did not bring the glucose down to as low a level as it did in the nonfasted rats. This seemed to indicate that something was protecting the fasting rats in this respect. Insulin in a low non-lethal dose injected into a fasted animal an hour before mescaline injection greatly increased the toxicity of mescaline and lowered the blood sugar more than did either mescaline or insulin alone. The injection of a non-lethal dose of epinephrine into nonfasted rats had no effect on the LD50 of mescaline although it seemed to protect the animal from the drastic blood sugar lowering and possibly modified the character of the terminal convulsions. These rats appeared to die of respiratory depression without the strong flexor convulsions. Mild clonic convulsions were noted at the time of respiratory failure instead. Artificially raising the blood sugar by injection of 5 per cent glucose before giving the mescaline, also had a protective effect against the hypoglycemic effect. Atropine also had a slight effect. Blood sugar in all experiments had returned to normal at the end of twenty four hours. Kerly et al (77) reported that they found twenty four hour fasting of male and female rats affected all metabolic changes. Insulin content of the pancreas and glycogen content of muscle was decreased. It is possible that the protective action of fasting on mescaline toxicity may be due, in part, to the presence of circulating epinephrine and, in part, to the decreased amount of insulin. Ellis (78) found that arylalkyl primary and secondary amines could attach to liver receptors which are usually sensitive to epinephrine, but that only those compounds possessing a catechol configuration could produce the hyperglycemic response. He, therefore, concluded that substances like mescaline could compete with epinephrine for the receptor, but because the OH groups on the benzene ring had been replaced by methoxy groups, the enzymatic reaction resulting in the release of glucose was blocked. If in addition to this type of reaction, the substance stimulates the release of insulin and simultaneous use of glucose, the reduction of blood sugar could be extreme.

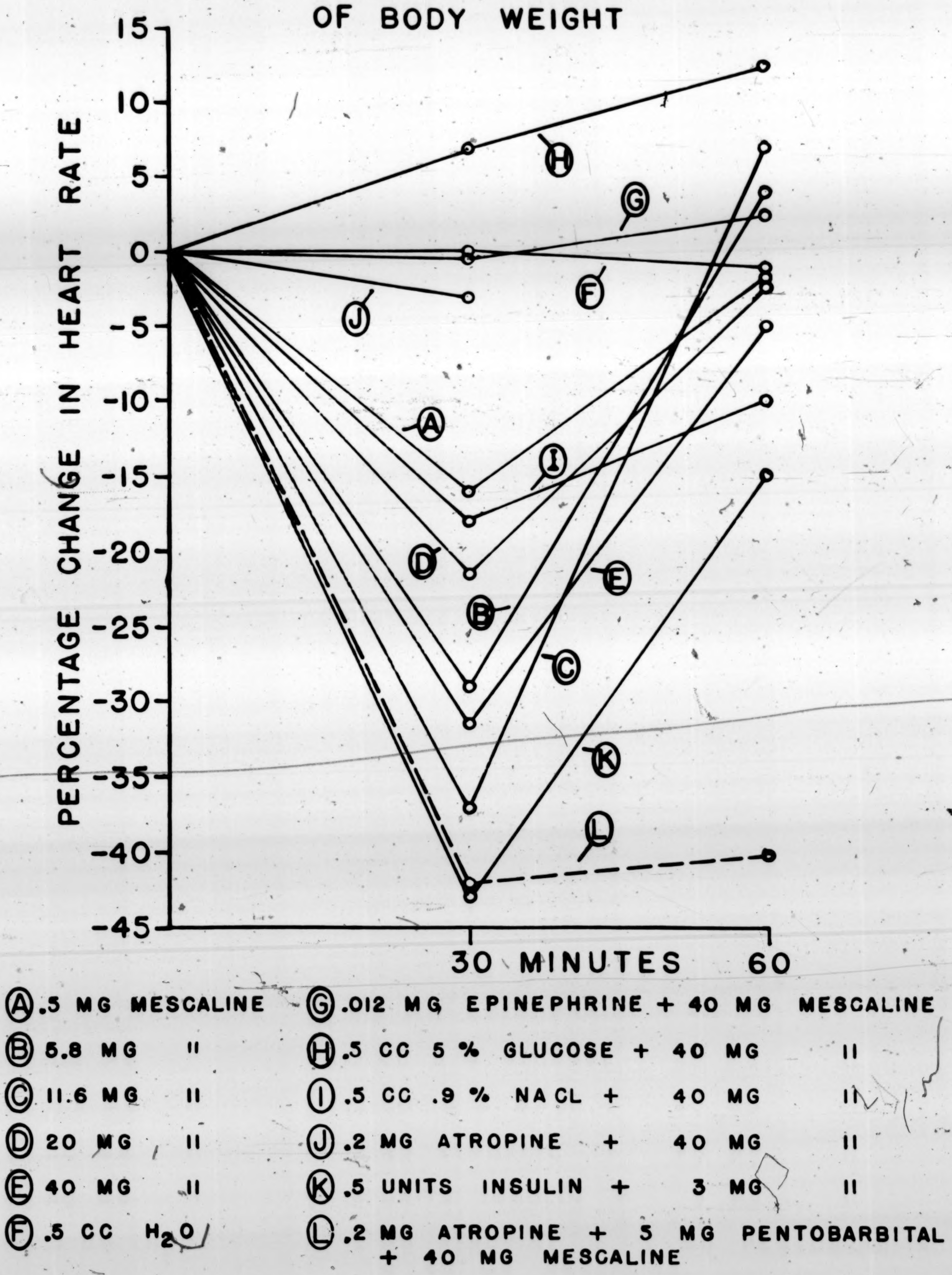
The same procedures were used to investigate the effect on heart rate. In this case the dose effect experiment had shown a maximum slowing at an intermediate dose. There was a falling off of the slowing at higher concentrations. Apparently, the increased slowing which appeared at LD50 doses was associated with failure of respiration. A previous injection of epinephrine had a 100 per cent protective action against the heart slowing produced by an LD50 dose of mescaline. The injection of glucose not only protected but produced an acceleration of heart rate. Atropine also had a protective effect but did not prevent all slowing. On the other hand, insulin markedly depressed the rate with only a small dose of mescaline and produced a great many irregularities in the rhythm. The 0.9 per cent NaCl which was injected as a control for the glucose loading experiments also had a mild protective action against mescaline in this respect. Grace (43) found that atropine did not block the heart slowing in anesthetized animals. He concluded that mescaline had a direct depressant effect on heart muscle since it slowed perfused hearts and arrested them in diastole. The slight increase in blood pressure observed in human beings, might contribute to central vagal stimulation. This component of the slowing of the heart by mescaline would be blocked by atropine. However, the fact that perfused hearts are slowed by mescaline suggests a direct action which is not blocked by atropine. Since a previous injection of epinephrine prevents the slowing of the heart rate, there is a possibility that mescaline may have an action similar in regard to the receptors as that proposed by Ellis (78) in regard to the liver.

A slight rise of blood pressure has been reported for mescaline in human beings (39). A pressor response has been reported for decapitated cats which was not blocked by ganglionic paralysis with nicotine. A depressor response has been reported in several kinds of anesthetized animals and in the decerebrate cat, which response is associated with respiratory depression. The last mentioned actions were completely blocked by atropine or section of the vagi. Grace (43), therefore, concluded that these effects were due to a central action of mescaline. In one experiment in which the mean arterial blood pressure was recorded by a direct method on a rat anesthetized with pentobarbital; intravenous injection of mescaline produced variable results. Under light anesthesia injections of mescaline resulted in a rise of blood pressure of 40 mm Hg. The same dose of mescaline caused first a decrease of 45 mm Hg followed by a sudden rise to 40 mm Hg above normal when the anesthesia was deepened. It appears that although mescaline does not have either a profound depressor or pressor effect that it would be worthwhile to investigate these phenomena further.

GRAPH I

SOME FACTORS INFLUENCING THE HEART RATE IN THE RAT

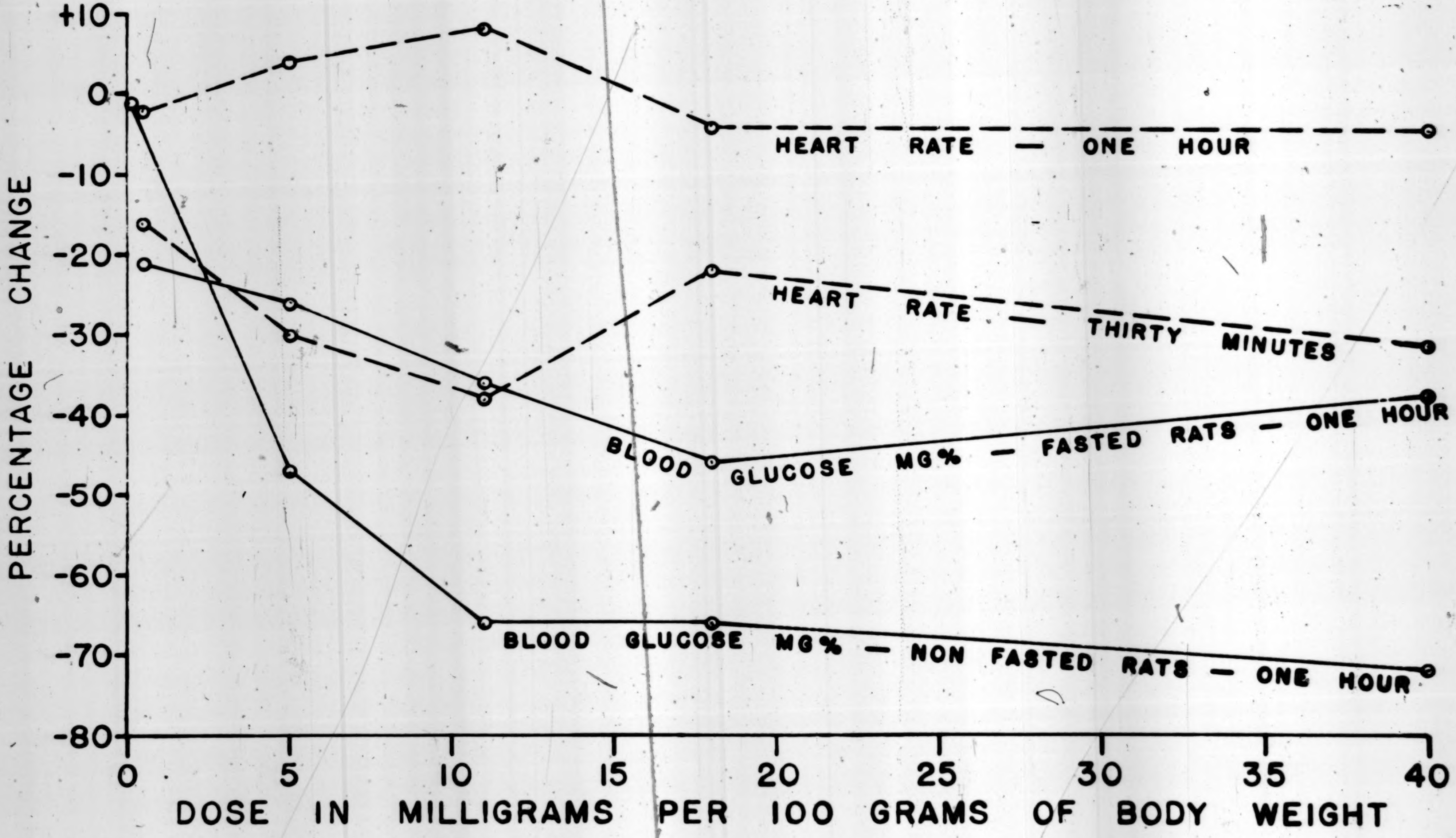
ALL DOSAGES GIVEN PER 100 GRAMS OF BODY WEIGHT



GRAPH II

EFFECT OF MESCALINE ON RAT BLOOD GLUCOSE AND HEART RATE

TIME GIVEN — AFTER INJECTION



ELECTROENCEPHALOGRAPHY:

The most conspicuous characteristic of the rat EEG was the great amount of low voltage fast activity present. This was only absent during pentobarbital anesthesia at the time of loss of the righting reflex. It was depressed by drowsiness and insulin. On the other hand, eserine, epinephrine, and mescaline markedly increased the low voltage fast activity. A frequency spectrum excluding low voltage fast activity showed a peak in the 9-15 cycles per second range in both the frontal and occipital leads. The 4-8 cycles per second activity was the next most frequent range found in both leads. There was more variation in the number of slow waves and low voltage fast waves present under different conditions than in either of the two intermediate ranges. The slow waves were checked against artifacts due to respiration, movement, sniffing, and nibbling, and were felt to represent true cortical activity. The fast waves were not depressed by muscle relaxants like curare and syncurine and did not appear to be the result of tremor or muscle tension. The results are tabulated below. Comparison of the drowsy, awake, and alert states showed alertness to be most associated with fast activity while drowsiness was associated with slow activity particularly in the frontals. Epinephrine did not produce the maximal fast activity but fell between the awake and alert records. Fasting for twenty four hours also gave an epinephrine-like record. The response seen after 0.5 mgm/100 gm dose of mescaline compares with the fasting record while results after a 20 mgm/100 gm dose more closely resemble those of epinephrine. However, in the latter case, the fast activity in the occipitals is associated with increased slowing in the frontal leads. Eserine is by far the most effective producer of fast activity. The insulin records were run to see how they would compare with the action of mescaline since hypoglycemia is present. The prevalence of slow waves in these records indicated that the central effects of mescaline are not due to hypoglycemia. Several records were also run with the rat and apparatus in a nitrogen atmosphere to see if anoxia may be a contributing factor. The record was predominantly slow under these conditions.

Marazzi (80), basing his statement on experiments conducted on the recorded activity from a transcallosal monosynaptic pathway in cat, says,

> "The suggestion that the effect of mescaline is secondary to cerebral anoxia resulting from the lowered blood pressure is untenable for the following reasons. Anoxia usually causes a transient enhancement of transmission before depression and this was not seen. When the blood pressure fall was exactly simulated by amyl nitrite no change in transmission was observed. Both mescaline and epinephrine cause inhibition of transmission though their effects on blood pressure are opposite."

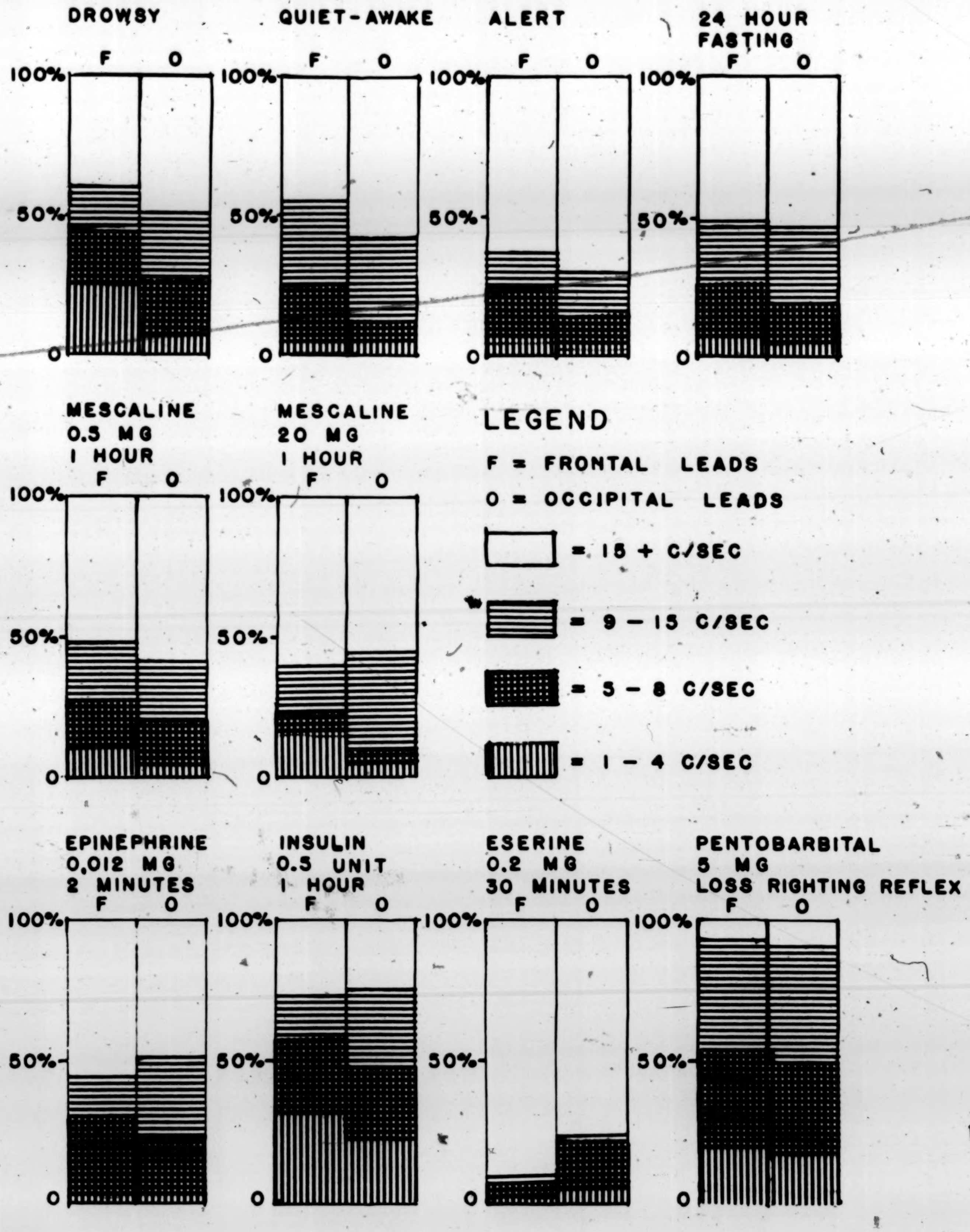
The same conclusions were reached for mescaline, amphetamine, and adrenaline (81). The degree of hypoglycemia present in mescaline intoxication would be expected to cause a slow record instead of a fast record. Gellhorn (82) reported that electroshock could restore the normal EEG of rats in the presence of blood sugars at coma levels. The possibility suggests itself that mescaline may have a specific stimulatory effect on that part of the brain which is affected by electroshock.

The response of the cerebral electrical activity of our animals to drowsiness, arousal, insulin, anoxia, pentobarbital, and convulsants was essentially the same as that found in other species and in human beings (83). Tsukiyama (84) described a relation between the central excitatory level and various drugs in rats. He found that a moderate dose of epinephrine

GRAPH III

RAT EEG UNDER VARIOUS CONDITIONS

AS PERCENTAGE – TIME DURATION OF FREQUENCIES
DOSES GIVEN PER 100 GRAMS BODY WEIGHT
TIME – AFTER INJECTION



suppressed the basic waves and increased the small fast wave activity. At somewhat higher levels spikes appeared and at still higher doses slow waves were seen. He concluded that the low voltage fast record was associated with an increased level of central excitatory state. Porter (85) found that epinephrine injections evoked increased spontaneous activity in the region of the posterior hypothalamus under cyclopropane anesthesia in cats and monkeys. He believed this to be a direct action as it is not abolished by decortication or transection of the lower brain stem. This response was not seen when the transection was at the level of the midbrain. Eosinopenia followed after a prolonged period. Dell et al (86) felt that epinephrine has both a facilitating and an inhibiting effect on the central nervous system. They found a facilitation of monosynaptic reflexes and increased spontaneous activity of motoneurons after intravenous epinephrine which was blocked by anesthetics and retromammillary transection. Inhibition of monosynaptic and polysynaptic reflexes and spontaneous activity was found after retropontine transection. However, this was replaced by facilitation after the roots of IX and X cranial nerves were cut, which eliminated among other things the afferent inflow from pressor receptors in the carotid sinus and the aorta. From these experiments they concluded that epinephrine exerts a direct and specific effect upon certain interneurons in the reticular formation of the brain stem, and that there may exist an integrative process in the central nervous system which is based on biochemical processes.

In contrast to these positive findings of increased electrical activity, Gottschalk (87) found no significant change in the EEG of human beings after injection of epinephrine using both cortical and basal leads. He also found no relation between the eosinophil response and the EEG. Leimdorfer (88) reported no alteration in the EEG of dogs after intracisternal injections of epinephrine as an anesthetic until large doses were reached, which depressed voltage. Marrazzi (81) suggested two mechanisms for the actions of sympathomimetic drugs; that they may exert a mixed action stimulating at some sites and inhibiting at others, or by inhibiting higher controlling cortical neurons thus releasing the activity of the lower cortical neurons. He felt that this was pertinent to the observation of the mental phenomena which are produced rarely with epinephrine, often with amphetamine, and conspicuously with mescaline. He found that the inhibition at the central synapses could be combated with acetylcholine and anti-cholinesterases and that atropine could block the effect. He did not feel that the inhibition was caused by change in cerebral blood flow or anoxia. There was indication that more was involved in the production of hallucinations than this inhibitory mechanism since epinephrine, which had the greatest blocking effect, does not often produce hallucinations. The observations of Osmond and Smythies (64) that adrenochrome is able to elicit these phenomena is interesting. Vicari et al (89) reported that epinephrine, glucose, and certain steroids protect susceptible mice from audiogenic convulsions which they assert is due to an inhibitory action in the auditory pathway by these substances. Gellhorn (66,p.411) suggested that although epinephrine at first acts as a powerful stimulant of the sympathetic system, its depressor effect on sympathetic ganglia may reduce discharges over the system and thereby contribute to homeostasis. This mechanism would be operative in emotional excitement and would have the tendency to restore hypothalamic reactivity to normal levels. He found that small amounts of adrenaline may temporarily inhibit metrazol convulsions. Ahlquist (29, 26/10) gives the central effect of epinephrine as follows: "It is not a true central stimulant although it possesses many qualities of these . . . it produces anxiety, apprehension, tremor, restlessness, and headache."

Although there is no complete agreement concerning the effects of epinephrine on the EEG, the findings of increased low voltage fast activity are consistent with many reports (84,85,88). At this time it is difficult to say whether these changes are the result entirely of a release phenomenon or of this action combined with stimulation and inhibition of specific pathways. In view of the latter possibility, the work of Chatfield (90) should be mentioned. This investigator found evidence of two acetylcholine sensitive systems in the cortex of the cat which had different thresholds to blocking and stimulation. The marked concentration of sympathin in the region of the posterior hypothalamus and the midbrain suggests a specific effect in this area (91). The possibility that there is direct stimulation of the posterior hypothalamus and its projections along with the release of subcortical centers by inhibition at a higher level should be considered.

The finding that twenty four hour fasting produced a record similar to that of epinephrine suggested that this is a result of stress. It has been mentioned previously that along with the moderately depressed blood sugar, there is a depletion of insulin in the pancreas and of glycogen in the muscle (77). Since fasted animals are so frequently used experimentally, these changes should be kept in mind.

Both low and high doses of mescaline produced similar effects on the EEG's. These records most closely resembled those obtained following epinephrine administration in that they were predominantly fast in character. However, a slowing which was greatest in the frontal leads (which pass through the motor cortex, end in the corpus callosum, and are over the caudate nucleus) indicates that these areas may be suppressed. The predominance of fast activity in the occipital leads (which pass through the visual cortex and end in the region of the posterior thalamic nucleus) suggests that these areas may be stimulated. Hyperactivity of the latter regions can not be considered as conclusive until the electrodes can be placed more precisely. Since these records in animals so closely resemble those in fasting and after epinephrine, the results were more easily seen in nonfasted and in quiet animals. These EEG results are consistent with the finding of abolition of alpha activity and the increase of low voltage fast activity which is found in human subjects under mescaline intoxication (37,60).

There is increasing evidence that there is a chemical specificity of neurons in various regions of the brain. Thus, the acetylcholine forming enzymes are in highest concentration in the caudate nucleus and in medullated fiber tracts (92). Substance P, a recently described polypeptide, also has this distribution but is never found together with acetylcholine (93). Acetylphosphatase, carbonic anhydrase, and succinic dehydrogenase are correlated with cell density (91). Raab's encephalin has its greatest concentration in the caudate nucleus and is lowest in white matter (79). This is in marked contrast to sympathin which is highest in the posterior hypothalamus, the medial thalamic nuclei, the midbrain and the anterior and posterior portions of the reticular formation. It is lowest in the caudate nucleus, the cerebellum, telencephalon, and all myelinated tracts (91). The hypothalamus is the only area in which high concentrations of all these substances coexist.

A number of drugs caused depletion of sympathin after three hours, such as apomorphine, insulin, nicotine, picrotoxin, and morphine, whereas metrazol, caffeine, ephedrine, and ergotamine have no effect. Vogt (91) suggested the possibility that the decrease of sympathin may be related to a lagging of synthesis after excessive demands of the stimulated cells for these amines. She further suggested that those amines may or may not be actual transmittors since they occur in nonganglionic tissue as well, but that they may modify transmission by other substances such as acetylcholine. Similar observations were made by Bülbring and Burn (94) concerning the action of epinephrine on acetylcholine effects at the level of the spinal cord. These people found that while a small dose of acetylcholine would cause a motor response, a larger dose would suppress the kneejerk and augment the flexor response. Eserine, prostigmine, and nicotine, all shared this characteristic. However, epinephrine while having no effect on the knee jerk, greatly augmented the flexor response to other drugs (94). There is at present no work showing that mescaline either augments or decreases brain sympathin. The flexor nature of the terminal convulsions resulting from a high dose of mescaline could be due to an epinephrine-like response to an increased acetylcholine concentration at the level of the spinal cord.

The parallel action of mescaline and sympathetic amines at central synapses suggests that these substances have a similar mode of action. However, the predominance of visual phenomena, the uncinate fits mentioned by Klüver, and the many symptoms characteristic of temporal lobe such as distortion of size, auditory hallucinations, and synesthesia, suggest that in addition to a general release of the subcortical structures as a result of central synaptic inhibition, there may be specific excitation of the occipital and temporal lobe areas and the projections to these areas.

EFFECT OF DRUGS ON ACTION OF MESCALINE:

Grace's (43) results with atropine have already been discussed fully. To summarize, he found that this drug blocked the blood pressure drop and the respiratory depression in anesthetized animals given mescaline. The heart slowing was not blocked in either the anesthetized intact animal or in the perfused heart. The blood pressure drop and respiratory inhibition were also blocked by cutting of the vagi in anesthetized animals. Although mescaline had no effect on isolated uterus or intestine, both of these tissues were strongly contracted in innervated preparations. This action was blocked by atropine. It was found by us that atropine in unanesthetized animals had a protective action against a part of the heart slowing but that this effect was not present under anesthesia. The results suggest that there is some excitatory influence coming down to the lower brain stem which is blocked by anesthesia and that the resulting excessive parasympathetic hypertonus can not be blocked by the usual doses of atropine.

The analeptic action of mescaline against a light dose of pentobarbital was noted early in the study. The slowed and spindling EEG record with light anesthesia was immediately replaced by low voltage fast activity after injection of any dose of mescaline. This resulted in arousal of the animal. Absolute insomnia has been reported by a number of investigators after administration of mescaline to human beings (2). An attempt was made to investigate the analeptic effect. The results of this investigation are tabulated below.

TABLE IV

COMPARISON OF MESCALINE AS AN ANALEPTIC WITH METRAZOL AND AMPHETAMINE

DOSE (mgm/100 gm body weight)	RECOVERY TIME (loss of righting reflex to recovery of reflex)	DEATHS
Pentobarbital 5mgm	83 minutes	0/4
Pentobarbital 5mgm Mescaline 5mgm	57 minutes	3/6
Pentobarbital 5mgm Mescaline 5mgm Atropine 0.2mgm	35 minutes	1/3
Pentobarbital 5mgm Atropine 0.2mgm	51 minutes	0/4
Pentobarbital 5mgm Metrazol 2mgm	57 minutes	0/5
Pentobarbital 5mgm Amphetamine 2mgm	88 minutes	1/5

Although these results are based on too few animals, it appears that any analeptic effect is offset by the toxicity of the drug in combination with pentobarbital. An LD50 dose of mescaline with this dose of pentobarbital is 100 per cent lethal while 5 mgm/100 gm dose of mescaline was always fatal with an LD50 dose of pentobarbital. Repeated injections of 1 mgm/100 gm doses of mescaline at twenty minute intervals both increased the toxicity and the length of wakening time. The investigation seems to indicate that mescaline is ineffective against barbiturate poisoning; the toxicity of both compounds appears to be increased, and repeated injections may be harmful. The analeptic action as concerns both the awakening and effect on the EEG suggests that mescaline may have a stimulating effect on the arousal centers of the posterior hypothalamus and the reticular formation of the midbrain. This is consistent with the reports of insomnia in human beings intoxicated with mescaline. The arousal center is one of the areas thought to be depressed by barbiturates. Intravenous sodium amytal has been suggested as an antidote for the psychic effects of mescaline but is alleged to have no effect on the autonomic effects (37).

Gellhorn (66) has mentioned that eserine and mescaline are synergistic in effect. The similarity between D.F.P. poisoning and some of the effects of mescaline has already been mentioned. Eserine in a dose of 0.1 mgm/ 100 gm resulted in 100 per cent survival in rats. Since eserine frequently caused bursts of multiple spike electrical activity with convulsions, a previous dose of Syncurine was given to prevent muscle artifact. Mescaline in a dose of 3 mgm/100 gm resulted in 100 per cent fatalities against this combination. Spike activity due to the eserine was decreased, and the rats rapidly died with gasping respiration, marked cyanosis, and peripheral vasoconstriction. Although an increase in convulsive activity had been anticipated, it was concluded that there was a synergism between eserine and mescaline in respect to the lethal effect. The decrease of spike activity could result from an increase of acetylcholine to such a level that it began to have an inhibitory effect at central synapses.

Although the dose of syncurine was such that the rat's body was relaxed during the convulsive stages of eserine, there did not appear to be any protection against the terminal flexor convulsion of mescaline. Experiments using mice and rats indicated that curare did not prevent the terminal flexor convulsions of mescaline. Subcutaneous doses of Regitine, 0.1 mgm/100 gm, were tried against mescaline in mice. This drug had no effect on the LD50 of mice although the terminal flexor convulsion appeared to be alleviated. These mice died of a gradual failure of respiration with gasping and cyanosis. Gernandt and Thulin (109) recently demonstrated that stimulation of the medial reticular formation was accompanied by increased ipsilateral flexor activity in the intact, unanesthetized cat. Stimulation of the lateral reticular formation produced increased extensor activity. Many of the effects of mescaline suggest that it may stimulate the reticular formation. In light of the investigation cited above, it appears possible that the flexor activity found after administration of large doses of mescaline may be the result of stimulation of the medial reticular formation. Because it was suspected that sulfhydryl enzymes might be involved, both cysteine and ascorbic acid were tried with an LD50 dose of mescaline. Neither substance had any effect on the lethal effects on rats although the nature of the convulsion was modified. Again, death appeared to result from the gradual failure of respiration.

The result of the experiments with insulin showed that this substance greatly increased the toxicity of mescaline. All doses of mescaline sulfate above 3mgm/100 gm proved to be 100 per cent lethal with any dose of insulin. Heart rate became excessively slowed and irregular. The blood sugar dropped precipitously. This substance was one of the most toxic when tried in combination with mescaline. Certainly, any derangement of insulin function should contraindicate any experimentation with mescaline intoxication.

Of all substances tested, only epinephrine itself had any protective action. The slowing of the heart and blood sugar drop was completely prevented. Even so, this substance did not change the LD50 in rats. The terminal convulsion was modified to a clonic type which accompanied respiratory failure. Respiration appeared to be gradually depressed until it ceased. The protective action of epinephrine given before mescaline suggests a competition for receptors peripherally. Although no person has ever died as a result of mescaline, and although this substance appears to be rather innocuous except at high doses, it would be well to consider the possibility that hormones and drugs may greatly increase the toxicity.

ELECTROLYTE EFFECT:

Tainter (62) reported that mescaline had a slight effect in raising the threshold to electric shock whereas most stimulants significantly lowered the threshold. Of all the central stimulants investigated by Tainter, only cocaine and mescaline raised the threshold. He suggested that the excitatory effect may be due to inhibition of inhibitory pathways. Doses of mescaline 5 mgm/100 gm were found to raise the threshold to electric shock by 2 MA. This heightened threshold was found a half hour after injection of mescaline at the time when heart rate is slowest. Since Woodbury and Davenport (74) found a relation between increased plasma level of sodium and increased threshold to electroshock, it was decided to investigate the blood levels of sodium and potassium after mescaline. The drugs were given to unanesthetized and unfasted rats. The results were as follows.

TABLE V

EFFECTS OF VARIOUS DRUGS ON Na^+ and K^+ BLOOD VALUES IN THE RAT
Doses Given as mgm/100 gm Body Weight

No.	Drug	Na^+ mEq/L	No.	K^+ mEq/L
11	none	148±2.12	3	4.3±0.18
5	1 mgm mescaline	141±1.71	5	4.5±0.12
5	20 mgm mescaline	139±7.87	too much hemolysis	
6	.012 mgm epinephrine i.p.	148±3.87	4	3.9±0.11
5	.025 mgm epinephrine subcut.	141±2.02	5	4.6±0.19
5	.1 mgm eserine i.p.	142±1.26	4	4.5±0.05

All samples were taken a half hour after injection which coincides with the time of maximal heart slowing, and of increase of threshold to electric shock. Only samples with minimal hemolysis were used for the potassium determinations. The higher dose of mescaline was always associated with increased coagulability and great hemolysis. All drugs except the control and intraperitoneal epinephrine appeared to reduce the plasma sodium level. However, this reduced level is closer to the normal figures given by Woodbury and Davenport (74) as 143 for sodium and 4.7 for potassium in rats.

Because of the smallness of the numbers the results are inconclusive. There does not appear to be any increase in sodium level as a result of mescaline administration to account for the increased threshold to electroshock, but in this group the great amount of hemolysis probably affected the determinations. Slocombe et al (95) suggest the possibility of at least two different kinds of increased convulsive activity, one based on sodium decrease and decreased threshold to electroshock, and another type which is not sodium dependent. Muirhead et al (96) found a decreased plasma sodium during continuous infusion of norepinephrine in dog. The electrolyte approach to the problem would be interesting to follow up since some of the effect of mescaline may be due to increased permeability of membranes: ie, marked hemolysis. Crescitelli (97) mentions a difference of response of different types of frog nerve fibers to sodium deficiency with the B fibers being most susceptible. Ussing (98) in in vitro experiments found that eserine, carbonic anhydrase inhibitors, 5 per cent CO_2, oxygen lack, cyanide, and dinitrophenol all decreased sodium transport across membranes from outside to inside. A number of pharmacologically different substances such as atropine, several curares, histamine, and pilocarpine all stimulated transport. There has been too little work with mescaline to form any opinion at this time as to whether its action has any relation to ion permeability.

CHRONIC EXPERIMENT:

The chronic experiment was carried out for a month and a half. Ten control rats were given 5 mgm mescaline per 100 gm rat daily. Both blood sugar and heart rate were somewhat elevated in the experimental group before injection of mescaline so that the actual effect of giving the drug brought the heart rate down to values seen in acute experiments at this dose while the blood sugars remained slightly higher than usual. There was apparently no tolerance developed to these actions although it seemed by observation that the period of cyanosis was decreased, and it did not seem to be as severe. Respiration decreased from 105 to 80 per minute. No unusual excitement was noted in the experimental group after the hyperexcitability of the first week had passed. There did not appear to be increased reaction to key-jangling, other noises, or touch. There was a difference between the behavior of the control and experimental animals at the time of the daily injections. The control animals were excited, but the others huddled in a far corner of their cage as though they were expecting an unpleasant experience although they had been acting normally when the room was entered. At the end of the experiment all the experimental group had ruffled coats, squealed when handled, and generally seemed more apprehensive. There was no increase in the incidence of spikes in the EEG's. The records were fast before injection and usually there was some slowing after injection as contrasted to the appearance of fast activity in the acute experiments. Examination of the viscera pointed to no outstanding consistent change with chronic administration of mescaline. Small hemmorrhages were noted in some of the lungs and in some of the livers of the chronic animals. In general, the veins appeared to be engorged, but no significant change in heart weight was noted. Samples of all these organs were sectioned and stained. No changes were noted in the kidneys or hearts. The livers of the rats who had received mescaline showed marked fatty infiltration. The increased weight of the adrenals appeared to be due to hyperplasia of the cortex. In general, the behavior, the slight increase of blood sugar, the rapid heart, and the increased size of the adrenals indicate that chronic mescaline intoxication has a "stressing" action on the animals. There does not seem to be any indication of increase in convulsive activity. Apparently in rats no tolerance was developed toward any of the effects of mescaline. No withdrawal symptoms were noted over weekends.

TABLE VI

RESULTS OF CHRONIC ADMINISTRATION OF MESCALINE

Categories	Controls	Experimental
Deaths	0/10	2/11
Mean body weight	240 gm	214 gm
Mean gain body weight during experiment	138 gm	124 gm
Mean weight liver	10.9 gm	11.2 gm
Weight liver/body weight	0.041	0.072
Mean weight adrenals (pair)	0.052 gm	0.072 gm
Weight adrenals/body weight	0.00022	0.00034
Mean weight heart	9.2 gm	8.3 gm
Weight heart/body weight	0.038	0.038
Average heart rate at end of experiment before daily injection	360/min	418/min
Average blood glucose at end of experiment before daily injection	95 mg%	110 mg %
Average heart rate $\frac{1}{2}$ hour after daily injection	360/min	228/min
Average blood glucose at end of experiment--1 hour after daily injection	93 mg%	76 mg %

CONCLUSIONS

Mescaline appears to have both peripheral and central effects. It cannot be decided from these experiments whether the fundamental agent is mescaline itself, a degradation product, or epinephrine. It is possible that all these agents are active at different sites. Thus, mescaline itself may compete for epinephrine receptors, while epinephrine may be responsible for some of the nervous system responses. The peculiar selectivity of the nature of the psychotic symptoms indicates that certain areas of the brain may be stimulated while others are inhibited. There appears to be more involved than a simple release mechanism due to inhibition at higher levels.

Mescaline seems to be an innocuous substance in low doses, however, there is evidence that other drugs and hormones may modify its toxicity. Chronic administration did not produce any specific and pronounced changes, other than evidence of a general stressing action. No tolerance or dependence was noted. Hoch, Pennes, and Catell say that mescaline psychosis probably consists of a complicated admixture of primary and secondary symptomatology in most or all individuals (99).

It is hoped that these experiments have thrown some light on possible mechanisms of mescaline action. In closing one could perhaps speculate that the action of this drug does not result in a mere depression of either the central or sympathetic nervous systems. The data suggest that an autonomic imbalance is produced. Vogt has mentioned the possibility that sympathin may have a modifying action on other transmittors such as acetylcholine. Bülbring and Burn also found evidence for this. Danziger and Elmergreen (100) worked out a mathematical theory of periodic relapsing catatonia. They concluded that the feedback system in the thyroxine-thyrotropin axis was oscillatory and spiral in nature. They could find no evidence that there was any defect in either the thyroid gland or the pituitary. Their calculations showed that there was a defect in the feedback system itself. The possibility arises that since epinephrine plays a modifying role in transmission as well as in homeostasis, that mescaline may disturb the sympathetic-parasympathetic equilibrium. It is possible that the rates of action of the enzyme systems associated with both epinephrine and acetylcholine may be the detector mechanisms in this feedback system, that this is the point at which mescaline produces its greatest effect and which causes it to produce psychotic states. In closing we quote from Hoch, "The further utilization of psychosis producing drugs as investigational tools will certainly continue to be fruitful as attention is directed more to the actual mechanisms of these drug reactions." (99).*

*Since this paper was written, Marrazzi in an article in Science, March 11, 1955 states, "The disturbance of adrenergic or related cerebral neurohumoral mechanisms appears to be implicated in the actions of the hallucinogens studied. The resulting imbalance in the reciprocal relationship between adrenergic inhibition and cholinergic excitation in the most susceptible cerebral synapses might be an underlying mechanism in mental disturbance."

SUMMARY

A number of experiments have been carried out for the purpose of investigating the pharmacological actions of mescaline. A summary of the results is listed below.

1. The intraperitoneal LD50 for nonfasted, male, albino rats was found to be 37mgm of synthetic mescaline sulfate per 100 grams body weight.

2. The effects of various doses of mescaline were studied and showed that there was a difference in action at different doses rather than an increase in effect as the doses were increased.

3. Factors varying the effects of mescaline were investigated. Insulin was found to increase the toxicity of mescaline while epinephrine was the only substance which could be said to decrease the toxicity: i.e. effect on heart rate and blood glucose. Even epinephrine itself was not effective in changing the LD50.

4. Electroencephalographic studies indicated that mescaline had an effect similar to epinephrine on cerebral activity.

5. The effect of different drugs on mescaline was observed.

6. Some preliminary investigation into the electrolyte effects was attempted. The results were inconclusive.

7. A chronic experiment was conducted which suggested that mescaline had a general stressing effect on the animals.

8. Some conclusions and speculations were discussed. It was felt that mescaline had both peripheral and central effects, that it paralleled

epinephrine in many of its actions, that it competed for epinephrine receptors, and that the specificity of its effects on cortical activity suggested that it may have a specific stimulatory effect on the reticular formation and its projections to the occipital cortex and temporal lobe, in contradistinction to a simple release of the brain stem as a result of inhibition of cortical synapses.

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